

REMARKS/ARGUMENTS

Claims 1-3, 7, 8, 12, 16, and 17 are pending.

The present invention relates to a method of treating brain edema by administering an effective amount of a composition comprising melatonin to a subject having brain edema.

See Claim 1.

The rejection of Claims 1-3, 7, 8, and 12 under 35 U.S.C. §102(b) over WO 97/20555 (hereinafter referred to as "WO '555") is respectfully traversed. The Examiner also cites U.S. 5,137,871 (hereinafter referred to as "U.S. '871") and U.S. 5,520,912 (hereinafter referred to as "U.S. '912") in support of the rejection (see page 3 of the Official Action dated December 2, 2003). WO '555 fails to disclose the claimed method.

Applicants submit herewith an executed Declaration from Dr. Kunio Torii. Dr. Torii is an inventor in the above-identified application. See paragraph (2) of the Declaration.

The field of the present invention is the pharmaceutical treatment of brain disorders. See paragraph (7) of the Declaration. Dr. Torii is an expert in that field. See paragraph (8) of the Declaration. He has worked in the field of the invention for more than 30 years and published many scientific articles as described in the *Curriculum Vitae* attached to the Declaration. See paragraph (8) of the Declaration.

According to Dr. Torii, there is no description in WO '555 of treating brain edema with melatonin. See paragraph (9) of the Declaration.

WO '555 describes a method for treating or preventing anoxic or ischemic brain injury by administering melatonin. See the Abstract of the reference and paragraph (10) of the Declaration. WO '555 does not mention brain edema at all. See paragraph (11) of the Declaration.

Brain edema is a condition in which excess fluid accumulates in brain tissue, which results in the swelling of the brain tissue. See paragraph (12) of the Declaration. That this is

so is demonstrated by the specification of the above-identified application at page 1, lines 14-16 and U.S. '871 at column 3, lines 39-43. See paragraph (12) of the Declaration.

Nowhere is it stated in WO '555 that the subjects described therein were suffering from the symptoms of brain edema described above. See paragraph (13) of the Declaration.

(11) It is true that ischemia is a cause of brain edema. See paragraph (14) of the Declaration. However, the fact that a subject has an ischemic brain injury does not mean that the subject must also have brain edema. See paragraph (14) of the Declaration. Thus, it is possible that a subject has an ischemic brain injury but does not have brain edema. See paragraph (14) of the Declaration.

In fact, there is no direct relationship between the clinical symptoms of ischemic patients and brain edema. See paragraph (15) of the Declaration. This makes the clinical effect of melatonin on the brain uncertain. See paragraph (15) of the Declaration.

The Examiner appears to agree with Applicants' position. See paragraph (16) of the Declaration. At page 3, lines 6-9 of the Official Action dated December 2, 2002, the Examiner stated:

Applicants argues that the subject has an ischemic brain injury does not mean that the subject has brain edema. **This might be true**; however, if a person has ischemia caused by brain edema, then by treating the ischemia, one is treating the edema also and instant claims do not exclude the condition. [Emphasis added.]

However, there is nothing in WO '555 which suggests that the subjects treated with melatonin as described therein were suffering from brain edema. See paragraph (17) of the Declaration. Therefore, the Examiner is only speculating that the subjects described in WO '555 were also suffering from brain edema, in addition to ischemia. See paragraph (17) of the Declaration. There is no evidence in WO '555 which supports the Examiner's speculation, since there is no mention at all of brain edema in that publication. See paragraph

(17) of the Declaration. Thus, the Examiner has failed to establish that the subjects described in WO '555 were necessarily suffering from brain edema. See paragraph (17) of the Declaration.

In addition, as shown at page 21 of WO '555, the mild 4-vessel occlusion model (which is also referred to as 4VO, 10 minute occlusion) was used to demonstrate the therapeutic efficacy in treating brain ischemia with melatonin. See paragraph (18) of the Declaration.

The 4VO model is not used by workers in the field of the invention to measure the therapeutic effect of an agent for treating brain edema. See paragraph (18) of the Declaration. This is because the 4VO model is well known in the field of the invention to suffer from a variety of problems relating to the identification of agents which are useful for treating brain edema. See paragraph (18) of the Declaration.

U.S. '871 describes a treatment to reduce edema for brain and musculature injuries. See the Abstract and paragraph (21) of the Declaration.

U.S. '871 at column 3, lines 39-51 states:

Brain edema refers to a condition in which there is increased water content in brain tissue. This condition occurs when there is a breakdown in the function of blood vessels that normally separate blood constituents from brain tissue. Brain blood vessels become more permeable when they are injured by a lack of oxygen, by toxic substances generated in injured tissues, or by unknown causes such as those associated with brain hemorrhage of the newborn. The medical conditions associated with brain edema are: brain ischemia, brain infarction, brain tumors, brain infarctions and abscesses, brain trauma and contusions, and secondary brain damage arising from neurosurgical operations.

Thus, a subject suffering from brain edema may also be suffering from brain ischemia. See paragraph (23) of the Declaration.

However, as noted above, the fact that that a subject is suffering from brain ischemia does not necessarily mean that the subject is also suffering from brain edema. See paragraph (24) of the Declaration. In other words, a subject may suffer from brain ischemia but not suffer from brain edema. See paragraph (24) of the Declaration. Again, as noted above, there is no direct relationship between the clinical symptoms of ischemic patients and brain edema. See paragraph (25) of the Declaration.

U.S. '912 describes the prevention and treatment of ischemic events and reperfusion injury resulting therefrom using Lys-plasminogen. See the Abstract and paragraph (26) of the Declaration.

At column 3, line 6 to column 4, line 6, U.S. '912 states that brain ischemia can cause brain edema. See paragraph (27) of the Declaration.

However, as discussed above, a subject suffering from brain ischemia does not necessarily also suffer from brain edema, i.e., a subject may suffer from brain ischemia but not suffer from brain edema. See paragraph (28) of the Declaration.

In view of the foregoing, WO '555 fails to describe, either explicitly or inherently, treating brain edema by administering melatonin to a subject having brain edema. Therefore, WO '555 fails to anticipate the claimed method. Withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 1-3, 7, 8, 12, and 16-17 under 35 U.S.C. §103(a) over WO '555 is respectfully traversed. WO '555 fails to suggest the claimed method.

As discussed above, WO '555 fails to describe treating brain edema by administering melatonin to a subject having brain edema. In fact, the reference fails to mention

In Dr. Torii's opinion, WO '555 would not have suggested a method of treating brain edema by administering melatonin to a subject having brain edema to one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in

the U.S. See paragraph (20) of the Declaration. That opinion is based on the facts that (a) a subject having an ischemic brain injury does not necessarily also have brain edema, (b) there is no direct relationship between the clinical symptoms of ischemic patients and brain edema which makes the clinical effect of melatonin on the brain uncertain. See paragraph (20) of the Declaration. Thus, one of ordinary skill in the field of the invention at the time the above-identified application was filed in the U.S could not have predicted with a reasonable expectation of success that melatonin could be used to treat brain edema based on the disclosure of WO '555. See paragraph (20) of the Declaration.

Based on the foregoing, the claimed method is not suggested by WO '555. Therefore, the claims are not obvious over that reference. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 1-3, 7, 8, 12, and 16-17 under 35 U.S.C. §103(a) over WO '555 in view of U.S. 4,687,763 (hereinafter referred to as U.S. '763) is respectfully traversed. Those references fail to suggest the claimed method.

As discussed above, WO '555 fails to describe or suggest the claimed method.

U.S. '763 describes a composition and method for increasing levels or release of brain serotonin. See the Abstract of the patent and paragraph (29) of the Declaration. The composition contains melatonin. See the Abstract and paragraph (29) of the Declaration.

U.S. '763 fails to describe or suggest administering melatonin to treat brain edema, since that patent fails to mention brain edema at all. See paragraph (30) of the Declaration. Therefore, U.S. '763 fails to remedy the deficiencies of WO '555 described above. In view of these facts, it is Dr. Torii's opinion that WO '555 taken in any combination with U.S. '763 fails to suggest a method of treating brain edema by administering melatonin to a subject having brain edema to one of ordinary skill in the field of the invention at the time the above-identified application was filed in the U.S. See paragraph (31) of the Declaration.

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Based on the foregoing, the claimed method is not suggested by WO '555 in view of U.S. '763. Therefore, the claims are not obvious over those references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.


Respectfully submitted,

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